Remarks

In view of the foregoing amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicants would like to point out that claims 1-13 and 15-43 remain pending and new claims 44-47 have been added. New claim 44 finds descriptive support at page 8, lines 4-9. New claim 45 finds descriptive support at page 7, lines 14-16 and original claim 4. New claims 46 and 47 find descriptive support at page 11, lines 4-5, and original claims 13 and 14, respectively. Therefore, no new matter has been entered.

Applicants would also like to point out the accompanying Information Disclosure Statement and references. Applicants respectfully request that the enclosed form PTO-1449 be initialled and signed, and then returned to applicants with the next response from the U.S. Patent and Trademark Office ("PTO").

The rejection of claims 1-43 under 35 U.S.C. § 112 (second paragraph) is respectfully traversed in view of the above amendments and the following remarks.

Applicants submit that claim 1 as amended clearly and unambiguously claims the subject matter the applicants regard as the invention.

Applicants further believe that one of skill in the art would clearly understand the claimed invention upon review of the specification. The specification candidly discusses the background to the invention and the most relevant art.

The present invention, as described on page 1 to 3 of the specification, builds on a previous invention of several applicants (*see* PCT Application Publ. No. WO96/38186 to Melrose et al. ("Melrose I") (copy attached to IDS)), in which it was found that poly(2-propenal, 2-propenoic acid) is formed when aldehyde groups of poly(2-propenal) are partially auto-oxidized to carboxylic acid groups by heating the compound (generally a solid) in air. The present invention relates to the finding that the antimicrobial activity and stability of the polymers of Melrose I are further significantly enhanced, i.e., the polymers are super-activated, by reacting them with organic compounds containing one or more hydroxyl groups (such as alkanols, phenols, polyols, etc.) under conditions effective to form a derivative of the starting polymer that is characterized by the presence of protected carbonyl groups (such as acetals or hemiacetals).

The finding of such super-activation was completely unexpected and indeed arose from tests carried out by the applicants which were intended to simulate accelerated aging of the polymer. This is explained on page 20, lines 1 to 13, of the present application. To the surprise of the inventors, the oxidized polymers not only aged well but also developed superior antimicrobial activity and stability. This superior activity and stability is due to the formation of protected carbonyl groups which form upon sustained heating of the previously oxidized acrolein polymer (i.e., the poly(2-propenal, 2-propenoic acid) of Melrose I) with organic compounds containing one or more hydroxyl groups. As explained on page 20, lines 25 to 28, the formation of protected carbonyl groups is believed to protect the polymers from alkaline degradation by the cannizarro reaction.

The formation of protected carbonyl groups is discussed in the present application and is explicitly demonstrated in Example 3. By monitoring proton magnetic resonance spectra of the poly(2-propenal, 2-propenoic acid), Example 3 demonstrates the formation of protected carbonyl groups (acetals in this example) as a result of reaction with an alcohol at 90°C for two hours.

The superior antimicrobial activity of the protected carbonyl derivative of poly(2-propenal, 2-propenoic acid) is also explicitly demonstrated in Example 2, Example 6 (*see* Table 7), Example 11, Example 12, Example 13, and Example 17. In each case, the protected carbonyl derivative of poly(2-propenal, 2-propenoic acid) is shown to have an activity that is significantly better than the oxidized but unprotected poly(2-propenal, 2-propenoic acid), which is the product of Melrose I.

Furthermore, not only does the present application demonstrate superior activity, but it also demonstrates reduced release of acrolein monomer from the protected carbonyl derivative. A reduction in the release of acrolein is particularly important and surprising because:

1. Acrolein monomer is an irritant for tissue and skin and can be toxic in high concentrations; and
2. Contrary to the demonstration in the present application, prior patents consider the activity of acrolein polymers to result from release of acrolein monomer (*see, e.g.*, U.S. Patent No. 6,060,571 to Werle et al. (copy enclosed with accompanying IDS), which is reviewed on page 3 of the present application).

Thus, in summary, the present application clearly demonstrates the formation of protected carbonyl groups by reaction with organic compounds containing one or more hydroxyl groups, as well as how formation of the protecting groups can be monitored in this context. This type of carbonyl protection will be generally familiar to organic chemists, who will be able to achieve protection of carbonyl groups with a range of organic compounds containing one or more hydroxyl groups as presently claimed.

The specification further demonstrates the significant improvement in activity of the carbonyl protected derivative of poly(2-propenal, 2-propenoic acid), and the reduction or elimination of the presence of the acrolein monomer irritant, which as noted above was previously considered by some to be the source of antimicrobial activity. These findings have enormous commercial significance in the fields of human and veterinary medicine, as the carbonyl protected derivative of poly(2-propenal, 2-propenoic acid) of the present invention is an antimicrobial of high activity and very good safety.

As the PTO will appreciate, resistance to conventional antibiotics has been widely reported as creating an emerging crisis in hospitals. This emerging crisis is caused to a large extent by use of traditional antibiotics in feed additives, particularly in the pig and poultry industries. The present invention provides an antimicrobial which is safe, and has increased activity and stability when compared with previously reported polyacrolein type antimicrobials. It also provides a real alternative to the use of conventional antibiotics.

From all of the foregoing, applicants submit that one of the ordinary skill in the art would fully comprehend the claim language of claim 1. Therefore, the rejection of claims 1-43 for indefiniteness is improper and should be withdrawn.

The rejection of claims 1-9, 12-23, and 43 under 35 U.S.C. 102(e) as anticipated by, or alternatively under 35 U.S.C. 103(a) for obviousness over, U.S. Patent No. 6,410,040 to Melrose et al. ("Melrose II") is respectfully traversed.

Applicants submit that Melrose is not available as prior art against claims 1, 3-7, 9, 10, and 13 because these claims find written descriptive support in parent U.S. Patent Application Serial No. 10/009,139, which is a national stage application based on PCT/AU00/00107, filed February 16, 2000 ("the '139 parent application") (copy attached as Exhibit A).

The limitations of claim 1 find descriptive support at page 5, line 20 to page 6, line 20 of the '139 parent application. Specifically, the cited passages describe the heating of poly(2-propenal, 2-propenoic acid) in the presence of polyethylene glycol or polyol or alkanol, all of which are organic compounds containing one or more hydroxyl groups. The protection and stabilization of carbonyl groups is described in the same cited passage and it is noted that such protection may occur via formation of acetals. Additional support appears in the examples, which describe preparation of claimed antimicrobials via the recited processes as follows: Examples 2, 3, and 7 (using polyethylene glycol 200 or 1000), and Example 5 (using ethane diol).

The limitations of claim 3 find descriptive support at page 6, lines 16-20, which indicates protection of carbonyls by acetal groups.

The limitations of claim 4 find descriptive support at page 4, lines 4-7, and page 6, lines 16-20, which recite the use of polyethylene glycol, polyol, or alkanol. Additional support for particular alcohols is recited in the Examples as noted above (*e.g.*, polyethylene glycol 200 or 1000 and ethane diol).

The limitations of claim 5 find descriptive support in the passages noted above with respect to claim 4 (reciting polyethylene glycol and polyols), Examples 2, 3, and 7 (using polyethylene glycol 200 or 1000), and Example 5 (using ethane diol).

The limitations of claim 6 find descriptive support in the passages noted above with respect to claim 4 (reciting polyethylene glycol), and Examples 2, 3, and 7 (using polyethylene glycol 200 or 1000).

The limitations of claim 7 find descriptive support in the passages noted above with respect to claim 4 (reciting polyethylene glycol), and Examples 2, 3, and 7 (using polyethylene glycol 200 or 1000).

The limitations of claim 9 find descriptive support in the passages noted above with respect to claim 4 (reciting polyethylene glycol), and Examples 2, 3, and 7 (using polyethylene glycol 200 or 1000).

The limitations of claim 10 find descriptive support at page 5, lines 12-18, which recites the use of the antimicrobials as preservatives, and at Example 8(b), which describes the use of the antimicrobial at a concentration of 300 ppm in a draft cooling tower containing water. In Example 8(b), the aqueous solution is the carrier and it is intended to be used for oral consumption, resulting in gastrointestinal administration.

The limitations of claim 13 find descriptive support in the passage and Example noted above with respect to claim 10.

Because claims 1, 3-7, 9, 10, and 13 are entitled to priority of the February 16, 2000 filing date, Melrose II is not available as prior art against these claims, and the rejection should therefore be withdrawn.

In addition to the foregoing, applicants submit that Melrose II fails to teach or suggest each and every limitation of the presently claimed invention.

Melrose II relates to processes for forming stable compositions of poly(2-propenal, 2-propenoic acid)—a product of Melrose I—that resist precipitation of the polymer under specified pH conditions. The method of Melrose II, as noted by the PTO at page 4 of the outstanding office action, involves dissolving poly(2-propenal, 2-propenoic acid) in an aqueous base, adding an organic compound containing one or more hydrophobic groups, and then acidifying the solution.

Aside from possibly using the same starting material as in the presently claimed invention, the composition of Melrose II is distinctly different from the antimicrobial of claim 1.

Polymerization of acrolein can occur by carbon-carbon polymerization (addition of unsaturated groups) or by carbon-oxygen polymerization. As a result, the backbone of the polyacrolein polymer chain includes carbon-carbon linkages (with aldehyde pendant groups) and carbon-oxygen linkages (with unsaturated or carbon-oxygen pendant groups). The hydrated, hemiacetal or acetal forms identified at column 1, lines 15-45 of Melrose II are clearly the groups formed in the backbone of the polymer upon polymerization of acrolein.

This is fully explained in Melrose I, which as noted above describes the preparation of poly(2-propenal, 2-propenoic acid) starting material. For example, claim 4 of Melrose I specifies the additional form as:

> "... the hydrated diol form, the hemiacetal or acetal form, as formed from the condensation of the diol form with the aldehyde or diol form, the tetrahydropyran or fused tetrahydropyran formed from condensation of the diol, the aldol-Michael self-condensation form...."

Thus, all of the forms contemplated result from the polymerization of acrolein via a mixture of carbon-oxygen and carbon-carbon mechanisms to form the polyacrolein backbone.

In contrast, the present invention of claim 1 relates to derivatives of poly(2-propenal, 2-propenoic acid) having protected carbonyl groups, the derivative being formed by reaction of the polymer with organic compounds containing one or more hydroxyl groups under conditions effective (i.e., appropriate time and temperature constraints) to form said derivative. Thus, the antimicrobial of the invention is derived from poly(2-propenal, 2-propenoic acid) and results from the formation of protected carbonyl groups at the *pendant* aldehyde and/or carboxyl groups present, *i.e.*, in the source polymer. Such derivatives may be pendant acetal or hemiacital groups formed from the pendent aldehyde and/or carboxyl groups present in the poly(2-propenal, 2-propenoic acid) polymer.

As noted above, Melrose II merely relates to the formation of a stable composition containing the product of Melrose I; whereas the presently claimed antimicrobial is a derivative of the product of Melrose I.

Because the process of making the presently claimed antimicrobial (i.e., heating the starting polymer at a sufficient temperature and for a sufficient amount of time in a solvent containing an organic compound having one or more hydroxyl groups, such as alcohols) differs from the Melrose

II process of forming a stable composition, it is improper for the PTO to infer that the product of Melrose II is the same as the claimed antimicrobial.

Moreover, the antimicrobial activity of the presently claimed antimicrobial differs from the antimicrobial activity of the product of Melrose I (which is contained in the composition of Melrose II). The activity of the presently claimed antimicrobial is tested side by side with the poly(2-propenal, 2-propenoic acid) of Melrose I (and, thus, Melrose II) in many examples provided in the present application. These examples show superior antimicrobial activity of the presently claimed antimicrobial, both *in vitro* and *in vivo*. Example 2 shows the superior activity in biocidal testing of the compounds of the invention (12 and 25 days heating at 60°C) compared with poly(2-propenal, 2-propenoic acid), the product of Melrose I which is contained in the stable compositions of Melrose II. *In vivo* testing in Example 11 shows the presently claimed antimicrobial to be three times more effective, than the poly(2-propenal, 2-propenoic acid) from which it is derived, in providing weight gain after 14 days in chickens. Because the microbial activity differs and Melrose II fails to teach or suggest that the process of preparing the compositions modifies the polymer of Melrose I contained therein, it is improper for the PTO to infer that the product of Melrose II is the same as the claimed antimicrobial.

In rejecting dependent claims 5-9, 23, and 43, the PTO at page 5 of the outstanding office action cites to Example 8 of Melrose II, suggesting that the method of forming the composition disclosed therein teaches the antimicrobial product as presently claimed. Applicants respectfully disagree.

As noted above, the presently claimed product is a derivative of poly(2-propenal, 2-propenoic acid) that has protected carbonyl groups (formed under effective reaction conditions between poly(2-propenal, 2-propenoic acid) and an organic compound having one or more hydroxyl groups). The stable composition formed in Example 8 of Melrose II does not provide conditions that would be effective for formation of the presently claimed derivative of poly(2-propenal, 2-propenoic acid). In particular, Example 8 of the Melrose II teaches the combination of poly(2-propenal, 2-propenoic acid) with PEG 1000 at 70°C. Once dissolved, NaOH micropellets were added and the solution stirred for 2 minutes. Thereafter, octyl methoxy cinnimate was added, followed by polymeric emulsifiers, while maintaining the temperature for an additional 15 minutes. The resulting composition was poured with stirring into room temperature water, effectively cooling the composition. Thus, the total amount of time that the composition remained at elevated temperature was about 17 minutes.

Based on results in Example 8 of the present application, albeit using PEG 200 rather than PEG 1000, it is highly improbable that the conditions of Example 8 in Melrose II would have been

effective to form the derivative of poly(2-propenal, 2-propenoic acid) as presently claimed. The reaction conditions (i.e., time and temperature) employed in Example 8 of Melrose II fall outside the windows defined in Example 8 of the present application. According to Example 8 of the present application, a reaction temperature of 70°C would require between 24 and 120 hours to obtain a product as presently claimed. Thus, the approximately 17 minutes at 70°C would not have been effective to form the derivative of poly(2-propenal, 2-propenoic acid) as recited in claim 1 of the present application.

Because Melrose II fails to teach or suggest the antimicrobial of claim 1, Melrose II cannot have taught or suggested any subject matter of claim 2-9, 12-23, and 43, all of which ultimately depend from claim 1.

For all these reasons, applicants submit that the rejection of claims 1-9, 12-23, and 43 as anticipated by, or alternatively for obviousness over, Melrose II is improper and should be withdrawn.

The rejection of claims 24-42 under 35 U.S.C. § 103(a) for obviousness over Melrose II is respectfully traversed. Because claim 1 is allowable over Melrose II for the reasons noted above, claims 24-42, which ultimately depend from claim 1, are likewise allowable over Melrose II. Therefore, the rejection is improper and should be withdrawn.

The rejection of claims 1-43 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,711,892 to Manoury et al ("Manoury") is respectfully traversed.

Manoury disclose 5-nitrofuryl derivatives of pyridylpropenoic acid hydrazides, which Manoury describes as being useful as antibacterial agents. However, the antibacterial agents of Manoury are very different from those defined in the claims of the present invention. As noted above, the antimicrobial of the claim 1 is a derivative formed by reaction between a poly(2-propenal, 2-propenoic acid) and an organic compound containing one or more hydroxyl groups under conditions effective to form the derivative having protected carbonyl groups. Unlike antimicrobials of the present invention, antibacterials of Manoury are *not* polymers. The integer m is either 0 or 1; there is no repeating unit. The antimicrobial of the present invention is a polymer containing 2-propenal and 2-propenoic acid units at least a proportion of which have been protected by the process recited in claim 1.

Because the presently claimed antimicrobial is neither taught nor suggested by Manoury, the rejection of claims 1-43 as anticipated by Manoury is improper and should be withdrawn.

The rejection of claims 1-43 under the judicially created doctrine of obviousness-type double patenting over claim 1-28 of Melrose II is respectfully traversed.

The analysis of an obviousness-type double patenting rejection parallels the analysis of an obviousness determination under 35 U.S.C. § 103 (*In re Braat*, 937 F.2d 589, 592-93, 19 USPQ2d 1289, 1292 (Fed. Cir. 1991)), however the analysis is limited to comparing the scope of the claims between the application and the cited patent (*see Manual of Patent Examining Procedure* § 804 (2001)).

Independent claims 1 and 18 are representative of the subject matter claimed by Melrose II.

Claim 1 of Melrose II recites a method for preparing compositions of poly(2-propenal, 2-propenoic acid) in aqueous base; adding an organic compound containing one or more hydrophobic groups, and subsequently acidifying the solution." As a consequence of these steps, the "interaction between the hydrophobic groups of the organic compound and the poly(2-propenal, 2-propenoic acid) prevents precipitation of the poly(2-propenal, 2-propenoic acid) occurring at pH $\geqq$ 5.5 and the solution is consequently stable over a broad pH range."

Claim 18 of Melrose II recites a composition that includes "poly(2-propenal, 2-propenoic acid) and an organic compound containing one or more hydrophobic groups" where "interaction between the hydrophobic groups of the organic compound and the poly(2-propenal, 2-propenoic acid) prevents precipitation of the poly(2-propenal, 2-propenoic acid) at pH $\geqq$ 5.5."

Thus, neither the method nor the composition claimed by Melrose II relates to the formation of a derivative of poly(2-propenal, 2-propenoic acid). Specifically, and for substantially the same reasons noted above, the invention claimed in Melrose II would not have resulted in the formation of a derivative of poly(2-propenal, 2-propenoic acid) having protected carbonyl groups. Moreover, neither the presently claimed product, nor its method of manufacture, would have been obvious over the stable composition of poly(2-propenal, 2-propenoic acid) of Melrose II and its method of preparation. As demonstrated above, the conditions recited for formation of the stable composition of Melrose II are deficient for forming the presently claimed antimicrobial derivative of poly(2-propenal, 2-propenoic acid). The conditions effective for formation of the claimed derivative (i.e., presence of the organic compound containing one or more hydroxyl groups and reacting under suitable conditions, such as time and temperature constraints) are neither taught nor suggested by any of claims 1-24 of Melrose II.

For these reasons, the rejection of claims 1-43 under the judicially created doctrine of obviousness-type double patenting over claim 1-28 Melrose II is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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